HOSPITAL ANTIBIOTIC TEAM POLICY

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Vancomycin Therapeutic Drug Monitoring (TDM) in Adult Patients

TITLE	Vancomycin Therapeutic Drug Monitoring in Adult Patients
SUMMARY	This document provides instruction and guidance to hospital personnel on how to manage Vancomycin Monitoring in Adult Patients in their ward or section.
	All Clinical Directors, Departmental Managers, Heads of Sections and Nursing Officers in charge of wards are required to instigate action to ensure the successful implementation of the policy within their area(s) of control.
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The finalisation of this guideline is pending approval by the Pharmacy & Therapeutics Committee

Vancomycin Monitoring in Adult Patients

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1. Aims of this guideline

These Guidelines are for the management of adult inpatients. **Vancomycin therapeutic drug monitoring (TDM) in paediatric patients is beyond the scope of this review.**
Parenteral vancomycin is indicated in Meticillin resistant *Staphylococcus aureus* (MRSA) invasive infection. Preferably with culture and sensitivity (C&S) result available, if not, after taking appropriate specimen for C&S.
This document is based on 'Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists' AJHSP, 66; Jan 2009 pp 82-98.

Please note oral vancomycin should not be used to treat systemic infections as it is not significantly absorbed from the GI tract and hence therapeutic drug monitoring is not necessary.

2. Background

The impurities in early formulations of vancomycin caused many of the adverse events.[1-4] However, routine monitoring and adjusting of serum vancomycin drug concentrations has been the subject of intense debate for many years.[5-9] Data derived from more recent studies advocate that vancomycin has little potential for nephrotoxicity or ototoxicity when used at conventional dosages (e.g., 1g every 12 hours [15 mg/kg every 12 hours]), unless it is used concomitantly with known nephrotoxic drugs or at very high dosages.[10-13]

3. Overview of vancomycin pharmacokinetic and pharmacodynamic properties

In patients with normal renal function, the α-distribution phase ranges from 30 minutes to 1 hour, and the β-elimination half-life ranges from 6 to 12 hours. The volume of distribution is 0.4–1 L/kg.[14-18]
Reports of the degree of vancomycin protein binding have varied, a level of 50–55% is most often stated.19,21 Penetration of vancomycin into tissues is variable and can be affected by inflammation and disease state. For example, with uninflamed meninges, cerebral spinal fluid vancomycin concentrations ranging from 0 to approximately 4 mg/L have been reported, whereas concentrations of 6.4–11.1 mg/L have been reported in the presence of inflammation.21 Penetration into skin tissue is significantly lower for patients with diabetes (median, 0.1 mg/L; range, 0.01–0.45 mg/L) compared with nondiabetic patients based on the median ratio of tissue vancomycin to plasma vancomycin concentrations (median, 0.3 mg/L; range, 0.46–0.94 mg/L).21 Vancomycin concentrations in lung tissue ranging from 5% to 41% of serum vancomycin concentrations have been reported in studies of healthy volunteers and patients.5,6,22,23 Epithelial lining fluid (ELF) penetration in critically injured patients is highly variable, with an overall blood:ELF penetration ratio of 6:1.[23,24]

4. Selection of pharmacokinetic and pharmacodynamic monitoring parameters

Reviews of pharmacokinetics/pharmacodynamics have recommended the AUC/MIC as the preferred parameter based in part on data from animal models, in vitro studies, and limited human studies.[6,25-28]
An AUC/MIC ratio of ≥400 has been recommended as a target to achieve clinical effectiveness with vancomycin.

5. Impact of dosing strategies on pharmacokinetic and pharmacodynamic parameters

Vancomycin dosages should be calculated on ABW. For obese patients, initial dosing can be based on ABW and then adjusted based on serum vancomycin concentrations to achieve therapeutic levels. [17] Continuous infusion regimens are unlikely to substantially improve patient outcome when compared with intermittent dosing.

6. Therapeutic vancomycin drug monitoring

Trough serum vancomycin concentrations are the most accurate and practical method for monitoring vancomycin effectiveness and should be obtained just before the next dose at steady state conditions
(Note: Steady-state achievement is variable but occurs approximately after the fourth dose.)

a. Optimal trough concentrations

Based on evidence suggesting that *S. aureus* exposure to trough serum vancomycin concentrations of <10mg/L can produce strains with VISA like characteristics, it is recommended that trough serum vancomycin concentrations always be maintained above 10 mg/L to avoid development of resistance.
Based on the potential to improve penetration, increase the probability of optimal target serum vancomycin concentrations, and improve clinical outcomes for complicated infections such as bacteraemia, endocarditis, osteomyelitis, meningitis, and hospital acquired pneumonia caused by *S. aureus*, total trough serum vancomycin concentrations of 15–20 mg/L are recommended. Trough serum vancomycin concentrations in that range should achieve an AUC/MIC of ≥400 in most patients if the MIC is ≤1mg/L.
In order to attain this target concentration for seriously ill patients, a loading dose of 25–30 mg/kg (based on ABW) can be considered. A targeted AUC/MIC of ≥400 is not achievable with conventional dosing methods if the vancomycin MIC is ≥2 mg/L in a patient with normal renal function (i.e., CLcr of 70–100 mL/min). Therefore, alternative therapies should be considered. Vancomycin dosages of 15–20mg/kg (based on ABW) given every 12 hours are required for most patients with normal renal function to achieve the suggested serum concentrations when the MIC is ≤1 mg/L. It should be noted that nomograms were not developed to achieve these targeted endpoints. Individual pharmacokinetic adjustments and verification of serum target achievement are recommended. When the dose exceeds 1g, (i.e., 1.5 and 2 g), the infusion time should be extended to 1.5 – 2 hours.

7. Vancomycin toxicity

There are limited data suggesting a direct causal relationship between toxicity and specific serum vancomycin concentrations. In addition, data are conflicting and characterised by the presence of confounding nephrotoxic agents, inconsistent and highly variable definitions of toxicity, and the inability to examine the time sequence of events surrounding changes in renal function secondary to vancomycin exposure. A patient should be identified as having experienced vancomycin-induced nephrotoxicity if multiple (at least two or three consecutive) high serum creatinine concentrations (≥50% increase from baseline, whichever is greater) are documented after several days of vancomycin therapy in the absence of an alternative explanation.

a. Role of therapeutic drug monitoring in preventing nephrotoxicity

Some investigators have found vancomycin therapeutic drug monitoring to be associated with decreased nephrotoxicity. Other factors associated with decreased toxicity include shorter courses of therapy, less total dosage in grams of the drug, and a decreased length of hospital stay.[7,12] However, Darko et al.[7] found therapeutic drug monitoring to be cost-effective only in patients in ICUs, those receiving other nephrotoxins, and, possibly, oncology patients.

Available evidence does not support monitoring peak serum vancomycin concentrations to decrease the frequency of nephrotoxicity. Monitoring of trough serum vancomycin concentrations to reduce nephrotoxicity is best suited to patients receiving aggressive dosing targeted to produce sustained trough drug concentrations of 15–20 mg/L or who are at high risk of toxicity, such as patients receiving concurrent nephrotoxins.
Monitoring is also recommended for patients with unstable renal function (either deteriorating or significantly improving) and those receiving prolonged courses of therapy (over three to five days). All patients receiving prolonged courses of vancomycin should have at least one steady-state trough concentration obtained (approximately after the fourth dose). Frequent monitoring (more than a single trough concentration before the fourth dose) for short-course therapy (less than five days) or for lower-intensity dosing (targeted to attain trough serum vancomycin concentrations below 15mg/L) is not recommended.
There are limited data to support the safety of sustained trough serum vancomycin concentrations of 15–20mg/L. When this target range is desired, obtaining once-weekly trough concentrations in haemodynamically stable patients is recommended. Frequent (in some instances daily) trough concentration monitoring is advisable to prevent toxicity in haemodynamically unstable patients. The exact frequency of monitoring is often a matter of clinical judgment.
Data on comparative vancomycin toxicity using continuous versus intermittent administration are conflicting and no recommendation can be made.

b. Incidence of ototoxicity & role of TDM

Monitoring serum vancomycin levels to prevent ototoxicity is not recommended because this toxicity is rarely associated with monotherapy and does not correlate with serum vancomycin concentrations. Monitoring may be more important when other ototoxic agents, such as aminoglycosides, are administered.

8. **Initial Investigations** .

Appropriate samples for culture and sensitivity +/- direct Gram Stain
Baseline blood, electrolyte, renal and liver tests.

9. Management

Continue therapy for the prescribed duration unless a relevant (25%) change occurs in any values. If clinical picture improves and: inflammatory markers return to normal; white cells are normal; and there is no sign of sepsis (e.g., low or high temperature) AND cultures are negative, consider stopping.
For CrCl <25ml/min wait for levels to be reported before the administration of subsequent doses

10. Dosing

Dosing: 15-20 mg/kg every 12 hours (based on ABW)
Seriously ill patients, a loading dose of 25–30 mg/kg
Dosing is based on ABW up to a maximum of 2g 12-hourly.
Where possible prescribe 12-hourly regimens at 10am and 10pm (convenient for patient and laboratory in terms of taking levels)

Infusion Time:
(1g/120 minutes; 1.5g/ 150 minutes; 2g/210 minutes)
The infusion must be given at a rate no greater than 10mg/min to prevent infusion related adverse effects.
Warning: Rapid infusion may lead to development of red man syndrome.
Other antibiotics (e.g. ciprofloxacin, amphotericin, rifampicin and teicoplanin) or other drugs that stimulate histamine release can result in red man syndrome. Discontinuation of the vancomycin infusion and administration of diphenhydramine can abort most of the reactions. Slow intravenous administration of vancomycin should minimize the risk of infusion-related adverse effects.

Patient's actual body weight	**Initial Dose**
>40<60 kg	≤1.0 g (over 120 minutes)
>60<80 kg	≤1.5 g (over 150 minutes)
>80 kg	≤2.0 g (over 210 minutes)

TDM: In unstable renal function, prolonged course, haemodynamically unstable patients -

In twice daily dosing:

Trough after 4th dose [just before 5th dose] (steady state).

In once daily dosing:

Trough after 2nd dose [just before 3rd dose] (steady state).

Target trough: 15-20mg/L (Note: This is no longer 10-15 µg/mL [update based on Am J Health Sys Pharm 66:82, 2009 & CID 49:325,2009]).

a. Dosing example 70kg adult with normal renal function

15mg/kg → 1050mg/dose rounded to 1g every 12 hours
20mg/kg → 1400mg/dose.
So any dose ranging between 1.0g to 1.4g is an appropriate initial dose and should lead to vancomycin levels in the range of 15-20mg/L. However, if levels fall either below the 15mg/L or above the 20mg/L threshold seek advice from the Antibiotic Team (Appendix 1) or MDH-Pharmacy (on extension 6504 Monday-Friday 07:30-15:00; Saturday 07:30-13:00 OR on extension 6514 during other times including Sundays and Public Holidays) for dose adjustment.

11. **Further investigations**
    Appropriate samples for culture and sensitivity +/- direct Gram Stain.

Twice weekly blood, electrolyte, renal and liver tests.

Twice weekly Vancomycin Levels and whenever there is a change in dose and/or frequency one has to wait again for steady state to be achieved.

Appendix 1:

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13. Summary (Quick Reference Guide)

Sampling Time:

Not needed in adult patients who:

- will be receiving vancomycin for ≤ 3 days
- are <60 years old, have normal body weight and stable renal function (ClCr >40 mL/min) and will be receiving vancomycin for ≤ 7 days.

No peak levels are to be taken.
Trough levels (within 30 minutes from the next due dose) at steady state (before the 5th dose in patients having 12-hourly dosing; before the 3rd dose in patients having 24-hourly dosing)

Dosing:

Patient's actual body weight	**Initial Dose**
>40<60 kg	≤1.0 g (over 120 minutes)
>60<80 kg	≤1.5 g (over 150 minutes)
>80 kg	≤2.0 g (over 210 minutes)

In seriously ill patients, a loading dose of 25–30 mg/kg

Maintenance dose: 15-20 mg/kg every 12 hours (based on ABW up to 2g/dose)

Where possible prescribe 12-hourly regimens at 10am and 10pm (convenient for patient and laboratory in terms of taking levels)

Dosing Interval:

Creatinine Clearance	**Dosing Frequency**
≥ 120 mL/min	8-hourly
<120 - ≥ 60 mL/min	**12-hourly**
<60 - ≥30 mL/min	24-hourly
<30 - ≥10 mL/min	48-hourly
<10 mL/min	96-hourly (based on trough level reaching 15mg/mL)
Haemodialysis	96-hourly (based on trough level reaching 15mg/mL)

Sampling Frequency:
Twice weekly and whenever there is a change in dose and/or frequency wait again for steady state to be achieved.

Therapeutic Range:
15-20mg/L